REMARKS

Claims 1-16, 36 and 37 presently appear in this case. Claims 17-26 have been cancelled without prejudice toward the continuation of prosecution in a divisional application. No claims have been allowed. The official action of January 28, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for activating natural killer cells in a human patient by administering an effective amount of an adenosine A3 receptor agonist (A3RAg). The agonist will activate the NK cells by fully or partially activating the adenosine A3 receptors on the NK cells. This method may be used to treat diseases that are sensitive to activated NK cells, such as the treatment of tumor cells, malignant and infectious diseases, immunoregulation, hematopoiesis, reproduction and neuroendocrine interactions.

The examiner has repeated the restriction requirement and made it final, stating that claims 17-26 have been withdrawn from further consideration as being drawn to a non-elected invention.

Claims 17-26 have been cancelled without prejudice toward the continuation of prosecution in a divisional application.

The examiner has objected to the disclosure due to an error in the name of Cl-IB-MECA.

The inconsistency in the name of the compound as set forth at various places in the specification is acknowledged, and the examiner is thanked for bringing this to applicant's attention. The correct formula of Cl-IB-MECA is 2-chloro-N^6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide. This was well known to the art as of the effective filing date of the present application, for example, from Yao et al, Biochem Biophys Res Comm 232:317-322 (1997), which was cited in the International Search Report, and a copy of which is attached to the Information Disclosure Statement filed on even date herewith. The same error appears in the specification with respect to the name of IB-MECA. This is also 3-iodobenzyl, as can be seen from the same reference. The specification and claims have now been amended so that every instance reads as was correctly set forth at page 13, lines 7-8, of the present specification.

The specification has also been reviewed for other typographical and clerical errors, and all such errors that have been noted have now been corrected. Reconsideration and withdrawal of this objection are, therefore, respectfully urged.

Claims 1-16 and 27-35 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for Cl-IB-MECA, does not reasonably provide enablement for methods to activate natural killer cells using any other A3RAg. The examiner states that undue

experimentation would be required to determine which A3RAg and what concentrations and specificity would be effective for activating natural killer cells. The examiner states that there is unpredictability in the art, and one working example is not sufficient to support the breadth of the claims. Further, with respect to claims 9-16, the examiner states that while the specification is enabling for methods to activate natural killer cells using Cl-IB-MECA, hence enabling methods to treat various tumor cells in which NK cells are known to be cytotoxic, does not reasonably provide enablement for methods for a therapeutic treatment of any other disease or symptom of a disease. This rejection is respectfully traversed.

With respect to the examiner's statement there is only a single working example in the specification, attached hereto is a Declaration under 37 C.F.R. §1.132 by the present inventor that describes results with two additional A3RAg's, IB-MECA and MRS1898. In addition, the specification mentions a number of other A3 agonists, for example, at page 8, line 19, to page 9, line 2. It can be seen from this Declaration that the present invention can readily be expanded to other agonists without undue experimentation. The art is aware of many A3RAg's. The present specification contains one example, and the attached Declaration two others. As three of these have been shown to be active, there is no reason to believe that any other A3RAg would not also be operable in the present invention, nor is there good reason to believe that undue

experimentation would be involved in order to determine appropriate dosages, etc. This is well within the skill of one of ordinary skill in the art without undue experimentation.

Regarding claims 9-16, claim 9 has now been amended in order to better define the disease treated by the method of the invention. It must be a disease that is sensitive to activated NK cells. Furthermore, the claim sets forth specific diseases and conditions that fall within this category. As the examiner concedes that NK cells may be activated by means of the present invention and the claims now only read on the treatment of diseases that are sensitive to activated NK cells, the claims are not broader than the enabling disclosure. Support for the amendments to claim 9 may be found on page 1, lines 5-17; page 5, lines 1-3; and the Examples. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 1-16 and 28 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that the term "individual" in claims 1-16 is indefinite as it is unclear if the individual is limited to humans, mammals, animals and/or cells. The examiner also states that the phrase "sulfur or carbon atom" in claims 2, 10 and 28 render the claims indefinite as Y cannot simply be a carbon atom, as that would imply a bivalent carbon.

The claims have now been amended to specify that the individual is a human being, and the phrase "sulfur or carbon atom" has now been amended to clarify that Y is an oxygen or sulfur atom or is CH_2. Accordingly, this rejection has now been obviated. Reconsideration and withdrawal thereof are, therefore, respectfully urged.

Claim 1 has been rejected under 35 U.S.C. §102(b) as being clearly anticipated by Williams. The examiner states that Williams teaches that 2-chloroadenosine, an adenosine receptor agonist stimulates natural killer cells. This rejection is respectfully traversed.

Claim 1 has now been amended to better define the invention and to specify that the A3RAg activates the NK cells via the A3 receptor, "so as to fully or partially activate adenosine A3 receptors on said NK cells and so as to achieve activation of said NK cells." In Williams, on the other hand, 2-chloroadenosine (2CA) acts on the NK cells via a novel non-A1/A2/A3 cell surface receptor. See the abstract, where it states:

> These data suggest that 2CA acts on NK cells via a novel (non-$A_1/A_2/A_3$) cell-surface receptor.

See also the paragraph bridging the left- and right-hand columns on page 190, the right-hand column on page 193, and the right-hand column on page 194. Furthermore, nowhere in Williams is it stated that 2CA is an A3 receptor agonist. On the contrary, reference is made to Barbieri et al, Neurochem

Int 32:493-504 (1998), a copy of the abstract of which is attached, which states that 2CA appears to bind to A2a receptors and not to A3 receptors. Thus, the agonist disclosed by Williams does not fall within the scope of claim 1, and Williams does not anticipate claim 1. Reconsideration and withdrawal of this rejection are, therefore, also respectfully urged.

Claims 27-35 have been rejected under 35 U.S.C. §102(b) as being anticipated by US patent 5,773,423 to Jacobson.

Claims 27-35 have now been deleted, thus obviating this rejection.

Claims 1-16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Williams and Jacobson. The examiner states that Williams teaches that 2CA is an adenosine receptor agonist that activates natural killer cells, but does not specifically teach Cl-IB-MECA. The examiner states that Jacobson teaches that modification of the adenosine at the 5' position and/or at the N^6- position will moderate A_3 selectivity and, therefore, it would be obvious to modify the 2-chloroadenosine of Williams to enhance the activation of natural killer cells. This rejection is respectfully traversed.

As stated above, the invention as defined in the presently amended claims teaches activation of NK cells by A3 agonists via the A3 receptor. Williams does not disclose the

method of the invention and, in fact, teaches away from the method of the invention in that he explicitly teaches that 2CA does not stimulate NK cells through the A3 receptor nor through any other adenosine receptor. One of ordinary skill in the art would, therefore, have had no reason to combine Williams with Jacobson since Jacobson teaches modification of adenosine to moderate A3 selectivity, while Williams teaches away from adenosine receptor binding. Accordingly, the method of the present invention would not have been obvious from any combination of Williams and Jacobson. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

The examiner states that the two Priebe et al publications teach that modulation of natural killer cells can be achieved via the adenosine A_1 or A_2 receptor. The examiner recognizes that these references do not implicate the adenosine A3 receptor and the activation of natural killer cells.

These and the other references of record have been noted, as has the examiner's implicit recognition that they are insufficiently pertinent to warrant their application against the claims. It is further noted that neither Priebe reference mentions A3 receptors at all. Furthermore, the results presented are not unequivocal (see the first full paragraph in the left-hand column on page 4331 of the first Priebe et al publication), and the authors summarize that the

mechanism of stimulation and inhibition may not involve adenosine receptors (page 4331, last paragraph in left-hand column and right-hand column).

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of Fishman, P.

Serial No. 09/832,818 Group Art Unit: 1623

Filed: April 12, 2001 Examiner: J. Young

For: **ACTIVATION OF NATURAL KILLER CELLS BY...**

DECLARATION
under Rule 132

Commissioner of Patents and Trademarks
Washington, D.C. 20231

I, Pnina Fishman, an Israeli citizen residing at 19 Asher Barash St., Herzliya, Israel, hereby declare:

1. I am currently the CSO of Can-Fite BioPharma.

2. My list of publications is attached herewith as Annex "A". My fields of expertise include the field of adenosine receptors and more specifically the A3 adenosine receptor and the development of agonists to this receptor as drugs for the treatment of cancer and inflammatory diseases.

3. I am familiar with the above captioned application (hereinafter "*the application*"), and with the claims thereof. The invention relates to a method for activating NK cells using one or more adenosine A3 receptor agonists (A3RAg).

4. Although the application describes results with Cl-IB-MECA, I believe that these results are representative of the A3RAg group in general. In the following, I describe experimental results using two additional A3RAg, IB-MECA and MRS1898.

5. In the first experiment, mice were treated with IB-MECA and the activity test of the NK was conducted *ex vivo* on the murine splenocytes, as described in the application (pages 13-14). It may be seen from Fig. 1 (Annex B) that IB-MECA induces NK activity *in vivo*.

6. In the second experiment, murine splenocytes were incubated with MRS1898 and the ^{51}Cr release assay was performed as described in the application. The results are presented in Fig. 2 (Annex C). It may be seen that only the low concentrations of 0.01, and 0.1 μM potentiate the NK activity,

demonstrating the specificity of A3RAg activation in the NK cells in response to the A3 agonist.

7. I therefore believe that these results support the claims of the application that A3RAg activate NK cells.

8. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 11, 2003

P. Fishman

Prof. Pnina Fishman

Annex A

Prof. Pnina Fishman, Ph.D.

LIST OF PUBLICATIONS

1. Djaldetti, M., Bessler, H., Fishman, P., Lewinski, U and Mandel, M.: Ultrastructural features of the white blood cells in the leukemias.Harefuah, 83:528-537, 1972.

2. Bessler, H., Fishman, P. and Djaldetti, M.: Phagocytic activity of Gaucher's cells. Harefuah, 86:173-177, 1974.

3. Djaldetti, M., Bessler, H., Fishman, P., Van der Lyn, E. and Joshua, H.: Ultrastructural features of the granulocytes in Down's syndrome.Scand. J. Haematol., 12:104-111, 1974.

4. Djaldetti, M., Mandel, E.M., Fishman, P., Bessler, H. and Lewinski, U. Intramitochondrial crystalline inclusions in metastatic hypernephroma of the liver. Biomedicine, 21:158-163, 1974.

5. Djaldetti, M., Fishman, P. and Pinkhas, J.: Ultrastructural alterations of the eosinophils in hypereosinophilic syndrome. Harefuah, 88:267-270, 1975.

6. Djaldetti, M., Bessler, H. and Fishman, P.: Hematopoiesis in the embryonic mouse spleen. II Alterations after phenylhydrazine administration to the mothers. Anatom. Record, 182:123-136, 1975.

7. Djaldetti, M., Ovadia, J., Bessler, H., Fishman, P., and Halbrech, I. Ultrastructural study of the erythropoietic events in human embryonic livers. Biol. Neonate, 26:367-374, 1975.

8. Djaldetti, M., Notti, I., Fishman, P. and Bessler, H.: Transfer of iron-dextran across the placenta. Acta Haematol., 53:292-299, 1975.

9. Djaldetti, M., Elion, D., Bessler, H. and Fishman, P.: Paroxysmal cold-hemoglobulinuria. Transmission and scanning electron microscopy features of erythrocytes. Am. J. Clin. Pathol. 63:804-810, 1975.

10. Djaldetti, M., Fishman, P. ____, Bessler, H. and Van der Lyn, E.: Corticosteroid effect on eosinophils in vitro: Ultrastructural studies. Haemotologia, 9:65-72, 1975.

11. Djaldetti, M., Bessler, H., Fishman, P. and Mactey, I.: Functional and ultrastructural studies of Sezary cells. Nouv. Rev. Fr. Hematol., 15: 567-574, 1975.

12. Agam, G., Gasner, S., Bessler, H., Fishman, P. and Djaldetti, M.: Chloramphenicol-induced inhibition of platelet protein synthesis: in vitro and in vivo studies. Brit. Jour. Haematol., 33:53-59, 1976.

13. Djaldetti, M., Bessler, H., Mandel, E.M., Weiss, S., Har-Zahav, L. and Fishman, P. Clinical and ultrastructural observations in primary acquired sideroblastic anemia. Nouv. Rev. Fr. Hematol., 15:637-648, 1975.

14. Mandel, E.M., Fishman, P., Kissin, E., Har-Zaav, L. and Djaldetti, M.: Intramitochondrial crystalline inclusions in the liver of a patient with hyperthyroidism. Acta Hepato-Gastroenterol., 23:182-, 1976.

15. Bessler H., Nothi, I., Fishman, P. and Djaldetti, M.: Erythropoietic events in cultured embryonic mouse spleen. Blood, 48:419-424, 1976.

16. Djaldetti, M., Bessler, H., Fishman, P., and Apostolov, K.: Erythroid precursor fusion induced by Sendai virus. Exp. Hemat., 5:27-40, 1977.

17. Fishman, P., Skutelski, E. and Djaldetti, M.: Ferritin phagocytosis. Arch. Path. Lab. Med., 101:100-102, 1977.

18. Korczyn, A.D., Fishman, P., Djaldetti, M. and Berginer, V.M.: Scanning electron microscope study of erythrocytes from patients with myopathy. Isr. J. Med. Sci., 13:131-133, 1977.

19. Djaldetti, M., Gafter, U. and Fishman, P.: Ultrastructural observations in myopathy complicating Cushing's disease. Am. J. Med. Sci., 273:273-277, 1977.

20. Agam, G., Van der Lyn, E., Fishman, P., Bessler, H., Noti, I. and Djaldetti, M.: Effect of cyclophosphamide on metabolic parameters of human platelets and polymorphonuclears. J. Reticuloendot. Soc., 21: 237-244, 1977.

21. Djaldetti, M. and Fishman, P.: Scanning and transmission electron microscopy study on the plasma cells of a patient with multiple myeloma. Acta Haematol., 58:173-180, 1977.

22. Lustig, S., Ascher, O., Fishman, P., Djaldetti, M. and Pluznik, D.H.: Correlation between movement concanavalin A membrane receptors and cytolysis. A scanning electron microscopy study. J. Cell Biol. 75: 388-397, 1977.

23. Djaldetti, M., Fishman, P., Bessler, H. and Apostolov, K.: SEM observations on Sendai virus - induced fusion of embryonic mouse erythroblasts. Exp. Hematol. 6: 321-326, 1978.

24. Djaldetti, M., Goodman, J. A. and Fishman, P.: Ultrastructure of the cells in the peripheral blood of human embryos at early gestational stages. Biol. Neonate, 33:177-183, 1978.

25. Djaldetti, M. and Fishman, P.: Satellitism of platelets to monocytes in a patient with hypogammaglobulinemia. Scan. J. Haematol. 21:305-308, 1978.

26. Djaldetti, M., Bessler, H. and Fishman, P.: Drug-induced platelet surface alterations. A possible mechanism for impaired aggregation. Hematologica, 63:531-547, 1978.

27. Djaldetti, M., Fishman, P. and Bessler, H.: The surface structure of Gaucher cells. Am. J. Clin. Pathol. 71:146-150, 1979.

28. Djaldetti, M., Fishman, P., Bessler, H. and Chaimoff, C.: pH-induced platelet ultrastructural alterations. A possible mechanism for impaired platelet aggregation. Arch. Surg. 114:707-710, 1979.

29. Djaldetti, M. and Fishman, P.: Relationship between mitochondrial location and migration of lymphocytes across the sinusoidal wall. J. Reticuloend. Soc. 26:135-141, 1979.

30. Djaldetti, M., Fishman, P., Bessler, H. and Notti, I.: SEM observations on the mechanism of platelet release from megakaryocytes. Thrombos. Haemostas. 42:611-620, 1979.

31. Djaldetti, M., Fishman, P. and Bessler, H.: Lectin-like effect of Echis coloratus venom on human and mouse lymphocytes. Exp. Hematol. 8: 200-206, 1980.

32. Lustig, S., Fishman, P., Djaldetti, M. and Pluznik, D. H.: Topographic changes of membrane receptors for wheat germ agglutinin during the cell cycles and their relation to cytolysis. Exp. Cell Res. 129:321-328, 1980.

33. Djaldetti, M. and Fishman, P.: The effect of aspirin on mouse small-intestinal mucosa - ultrastructural studies. Arch. Pathol. Lab. Med. 105:144-147, 1981.

34. Fishman, P., Djaldetti, M. and Pluznik, D. H.: Scanning electron microscope observations on surface changes occurring in murine granulocytes and macrophages during maturation in soft agar cultures. Exp. Haematol., 9:628-636, 1981.

35. Fishman, P., Levi, J., Notti, I. and Djaldetti, M.: Synthesizing activity and ultrastructural findings of human blood cells after incubation with cis-platinum "in vitro". Biomedicine, 34:78-82, 1981.

36. Djaldetti, M., Fishman, P., Notti, I. and Bessler, H.: The effect of tetracycline administration on iron absorption in mice. Biomedicine, 35:150-152, 1981.

37. Djaldetti, M. and Fishman, P.: SEM and TEM studies on the osmotic behaviour of control and leukemic lymphocytes and polymorpho-nuclears. Virchows Archiv. B. Cell. Pathol. 40:39-50, 1982.

38. Djaldetti, M., Fishman, P., Creter, D. and Notti, I.: Ultrastructural and functional studies on human platelets incubated with diclofenac sodium (Voltaren). Acta Haematol., 68:285-294, 1982.

39. Djaldetti, M., Fishman, P., Cohen, A., Roffman, E., Levinsky, H., Glaser, M. and Zahavi, I.: Effect of diclofenac-sodium (Voltaren) on the electrical charge of human platelet membrane. Acta Hematol. 70:296-301, 1983.

40. Katz, S., Klein, B., Elian, I., Fishman, P. and Djaldetti, M.: Phagocytic activity of monocytes from diabetic patients. Diabetes Care, 6:479-482, 1983.

41. Fishman, P., Zahavi, I. and Djaldetti, M.: In vitro colony-forming cells in embryonic mouse liver, spleen and peripheral blood. Acta Haematol. 71:356-358, 1984.

42. Glaser, T., Fishman, P., Klein, B., Levi, J. and Djaldetti, M.: Generation of superoxide anions during phagocytosis by monocytes of uremic patients. Nephron, 38:40-43, 1984.

43. Fishman, P., Sredni, B., Hart, J. and Djaldetti, M.: Elemental x-ray microanalysis of mouse peritoneal and bone marrow derived cultured mast cells. Ann. Allergy, 53:70-73, 1984.

44. Mittelman, M., Fishman, P. and Djaldetti, M.: Effect of human saliva on the phagocytic activity of polymorphonuclear leukocytes and monocytes. Biomed. and Pharmacotherapy, 38:171-175, 1984.

45. Weinstein, T., Fishman, P., Klein, B., Levi, J. and Djaldetti, M.: Effect of cimetidine on granulocyte-macrophage colony formation by normal and chronic renal failure bone marrrow cells. Kidney Intern. 26:741-743, 1984.

46. Djaldetti, M., Fishman, P., Chaimoff, C., Kessler, E., Mittleman, M. and Hart, J.: Severe alterations of red blood cells from the vessels of colorectal tumors. Arch. Pathol. Lab. Med. 109:62-64, 1985.

47. Fishman, P., Djaldetti, M., Hart, J. and Sredni, B.: Growth of human basophil lines derived from chronic myelocytic leukemia cells in vitro: Ultrastructure and X-ray microanalysis. Immunology, 55:105-113, 1985.

48. Chaimoff, C., Fishman, P., Hart, J. and Djaldetti, M.: Transformation of erythrocytes to spherocytes following incubation with malignant cells. J. Submicrosc. Cytol. 17:465-468, 1985.

49. Fishman, P., Hart, J. and Djaldetti, M.: X-ray microanalysis of normal human neutrophils, lymphocytes, monocytes and platelets. Biomed. & Pharmacotherapy, 39:389-392, 1985.

50. Djaldetti, M., Fishman, P., Creter, D., Zahavi, I., Zevin, D. and Levi, J.: Platelet X-ray microanalysis in patients with chronic renal failure. Acta Haematol. 74:213-217, 1985.

51. Zahavi, I., Notti, I., Fishman, P. and Djaldetti, M.: The effect of nifedipine on protein synthesis and surface morphology of peripheral blood cells. Nouv. Rev. Fr. Hematol. 28:3-6, 1986.

52. Djaldetti, M., Fishman, P., Zahavi, I., Hart, J. and Chaimoff, Ch.: Surface ultrastructure of colorectal carcinoma cells. Colo-proctology, 8:48-51, 1986.

53. Strausberg-Djaldetti, R., Fishman, P., Bessler, H. and Djaldetti, M.: The effect of propranol on protein synthesis and phagocytosis by polymorphonuclear leucocytes from newborn, children and elderly individuals. Biomed. & Pharmacotherapy, 40:256-269, 1986.

54. Mittleman, M., Fishman, P. and Djaldetti, M.: Reduced phagocytosis-promoting activity of saliva from patients with chronic lymphocytic leukemia. Biomed. & Pharmacotherapy, 40:308-311, 1986.

55. Djaldetti, M., Fishman, P., Harpaz, D. and Lurie, B.: X-ray microanalysis of the fingernails in cirrhotic patients. Dermatologia, 174:114-116, 1987.

56. Djaldetti, M., Fishman, P. and Hart, J.: The iron content of fingernails in iron deficient patients. Clinical Science, 72:669-672, 1987.

57. Sirota, L., Straussberg, R., Fishman, P., Dulitzky, F. and Djaldetti, M. X-fingernails in term and preterm infants. Pediatric Dermatology, 5:184-186, 1988.

58. Djaldetti, M., Gilgal, R., Fishman, P. and Zahavi, I. Effect of Verapamil on platelet surface ultrastructure and calcium content. Acta Haematol.,79:41-43, 1988.

59. Fishman, P., Sredni, B. and Djaldetti, M. Recent advances in interleukin-3 research: A review. Israel J Med Sci., 26(7):414, 1990.

60. Fishman, P., Djaldetti, M., Sofer, Y., Grossman, S. and Sredni, B.: Spontaneous release of a factor with interleukin-3-like activity by human lymphocytes and monocytes. Nat. Immun. Cell Growth Regul., 9:334, 1990.

61. Djaldetti, R., Fishman, P., Shtatlender, V., Sredni, B. and Djaldetti, M. Effect of dexamethasone on IL-1 and IL-3-LA release by unstimulated human mononuclear cells. Biomedicine & Pharmacol., 44:515-518, 1990.

62. Fishman, P., Sredni, B. and Djaldetti, M.: Relation between interleukin-3 and basophil production in chronic myeloid leukemia patients. Immun. Letters, 28:73-78, 1991.

63. Sredni, B., Fishman, P., and Albeck, M. New Chemical Immunomodulators. McGraw-Hill Yearbook of Science and Technology. 195-197, 1991.

64. Fishman, P., Sheonfeld, Y., Djaldetti, M. and Sredni B. Interleukin-3-Like activity levels in pregnant women: Possible modulation by progesterone. J. of Reprod. Immunol., 22:211-216, 1992.

65. Bakimer, R., Fishman, P., Blank, M., Hohmman, A., Sredni, B., Djaldetti, M. and Shoenfeld, Y. Induction of Primary Anti-Phospholipid Syndrome in Mice by Immunization with a Human Monoclonal Anti-Cardiolipin Antibody (H-3): The Putative Role of Cytokines. J. Clin. Invest. 89:1558-1563, 1992.

66. Fishman, P., Bakimer, R., Blank, M. and Sheonfeld Y.: The putative role of cytokines in the induction of primary anti-phospholipid syndrome in mice. Clinical and experimental Immun. 514:495, 1992.

67. Fishman, P., Sredni, B., Hart, J. and Djaldetti, M. Cultured human cord blood cells spontaneously produce a factor with basophil-promoting activity. Immun. Letters.34:189-194, 1992.

68. Fishman, P. and Shoenfeld, Y. : Vitiligo as an autoimmune disease. Harefuah, 123:339-341, 1992.

69. Fishman, P., Falach-Vaknine, E., Zigelman, R., Bakimer, R., Sredn, D., Djaldetti, M. and Shoenfeld Y. Prevention of fetal loss in experimental anti-phospholipid syndrome by in vivo administration of recombinant Interleukin-3. J. Clin. Invest. 91:1834-1837, 1993.

70. Fishman, P., Shoenfeld, Y., Azizi, E., Sredni, B., Yecheskel, G., Zigelman, R., Floro, S. and Djaldetti, M. Vitiligo antibodies are effective against melanoma cells. Cancer 1993.

71. Fishman, P and Shoenfeld, Y. Cytokines, Interleukine-3 and Autoimmunity. Israel J Med Sci. 29:159-164, 1993.

72. Fishman, P., Nedivi, R., Djaldetti, M., Sredni, B., Kayzer, S. and Chaimoff, C. Kinetics of cortisol, IL-2 and IL-3-LA levels following surgical intervention. Nat. Immun. Cell Growth Regul. 12:35-40, 1993.

73. Weinstein, T., Fishman, P., Djaldetti, M. and Levi, J. Cytokine production by mononuclear cells derived from patients with chronic renal failure and patients on Hemo and peritoneal dialysis. Israel J Med Sci., 29:183-186, 1993.

74. Fishman, P., Kamashta, M., Ehrenfeld, M., Vianna, J., Hughes, GRV., Sredni, D., Zigelman, R., Sabo, G. and Shoenfeld, Y. Interleukin-3 Immunoassay in SLE patients-Preliminary Data. Inter. Arch. Allergy and applied Immunology. 100:215-218, 1993.

75. Winder, A., Fishman, P., Djaldetti, M. and Cohen, AM. The effect of Alpha Interferon on Thymidine, Uridine and Leucine uptake, and ultrastructure of the peripheral blood mononuclear cellls from Multiple Myeloma patients. Biochemical Med & Metabolic Biol. 49:124-132, 1993.

76. Fishman, P. and Shoenfeld Y. Lessons from experimental anti-phospholipid syndrome (APLS). Seminars in Clinical Immunology. 6:39-46, 1993.

77. Merimsky, O., Shoenfeld, Y., Yecheskel, G., Chaitchik, S., Azizi, E. and Fishman, P. Vitiligo-and melanoma-associated hypopigmentation: a similar appearance but a different mechanism. Cancer Immunol. Immunother. 38:411-416, 1994.

78. Fishman, P. Autoimmunity and Cancer. Israel J Med Sci., 29: 55-59, 1993.

79. Shoenfeld, Y. and Fishman, P. Role of IL-3 in the Antiphospholipid Syndrome. Lupus 3, 259-261, 1994.

80. Merimsky, O., Shoenfeld, Y., Chaitchik, S., Yecheskel, G. and Fishman, P. Antigens and Antibodies in Malignant Melanoma. Tumor Biol. 15:188-202, 1994.

81. Orvieto, R., Voliovitch, I., Fishman, P. and Ben-Rafael, Z. Interleukin-2 and ovarian hyperstimulation syndrome: a pilot study. Human Reproduction 10:24-27, 1995.

82. Djaldetti, R., Achiron, A., Ziv, I, Djaldetti M., Fishman, P. IL-3 production by mononuclear cells of patients with multiple sclerosis. Immunol Invest 24: 765-773, 1995.

83. Fishman, P., Falach-Vaknin, E., Sredni, B., Meroni, P.L., Rudniki, C. and Shoenfeld Y. Aspirin modulates interleukin-3 production: additional explanation for the preventive effects of aspirin in antiphospholipid antibody syndrome. J. of Rheumatology, 22:1086-1090, 1995.

84. Shoenfeld, Y., Blank, M. and Fishman, P. Antiphospholipid syndrome: from the laboratory bench to the patients' bedside. Lupus 1:S33-S36, 1995.

85. Baharav, E., Merimsky, O., Shoenfeld, Y., Altomonte, M., Maio, M., Ferrone, S. and Fishman, P. Anti-tyrosinase antibodies participate in the immune response to vaccination with anti-idiotypic antibodies mimicking the high-molecular-weight melanoma-associated antigen. Melanoma Research 5: 337-343, 1995.

86. Tomer, Y., Gilburd, B., Blank, M., Lider, O., Hershkoviz, R, Fishman, P., Zigelman R., Meroni, PL., Wiik, A. and Shoenfeld, Y. Characterization of biologically active ANCA induced in mice: pathogenetic role in experimental vasculitis. Arthritis & Rheumatism 38:1375-1381, 1995.

87. Sirota, P., Schild, K., Elizur, A., Djaldetti, M. and Fishman, P. Increased interleukin-1 and interleukin-3 like activity in schizophrenic patients. Prog. Neuro Psychopharmacol & Biol Psychiat.19:75-83, 1995.

88. Fishman, P. and Shoenfeld, Y. Cytokines in the Antiphospholipid Syndrome. The Antiphospholipid Syndrome. CRC Press, Inc. 1995, Chapter in Book.

89. Fishman, P., Falach-Vaknin, E., Sredni, B., Meroni, P.L., Timcamo, A., Dicke,r D. and Shoenfeld, Y. Aspirin-interleukin-3 interrelationships in patients with anti-phospholipid syndrome. American J. Reproductive Immunol. 35:80-84, 1996.

90. Fishman P. and Shoenfeld Y. Aspirin, interleukin-3 and antiphospholipid syndrome. Isr. J. Med. Sci. 32:13-17, 1996.

91. Djaldetti, M., Sredni, B., Zigelman R., Verber, M. and Fishman, P. Muscle cells secrete a low molecular weight factor with anti-cancerous activity. Clin. Exp. Metastasis 14:189-196, 1996.

92. Merimsky, O., Shoenfeld, Y., Baharav, E., Altomonte M, Chaitchik S, ,Maio M, Ferrone S, Fishman, P. Melanoma associated hypopigmentation: Where are the antibodies? American Journal of Clinical Oncology 19: 613-618, 1996.

93. Baharav, E., Shoenfeld, Y., Merimski, O., Zigelman R., Gilbrud, B., Yecheskel, G., Youinou, P. and Fishman, P. Tyrosinase as an autoantigen in patients with vitiligo. Clin. Exp. Immunol. 105:84-88, 1996.

94. Fishman, P. and Shoenfled Y. Cytokines in the Antiphospholipid Syndrome The Antiphospholipid Syndrome, CRC Press, Chapter 7: 83-88, 1996.

95. Fishman, P., Merimsky, O., Baharav, E. and Shoenfeld, Y. Tyrosinase Autoantibodies. Text book of Autoantibodies, Elsevier Press Inc. 842-845, 1996.

96. Kayzer, S., Myslovaty, B., Fishman, P., Gelber, E., Zigelman, R., Rudnicki, C. and Chaimoff, C. Cytokine profile in experimental biliary obstruction. Chirurgisch Gastroenterologie 12:153-156, 1996.

97. Merimsky, O., Baharav, E., Shoenfeld, Y., Chaitchik, S., and Fishman, P. Anti-tyrosinase antibodies in malignant melanoma. Cancer Immunol. Immunother. (5): 297-302, 1996.

98. Baharav, E., Gur, H., Fishman, P., Ziporen, L., Blank M., Aelion J., Kotb, M. and Shoenfeld Y. Superantigens and experimental SLE induced by idiotypic dysregulation. Clin. & Exper Rhumatol 14: 359-366,1996.

99. Merimsky, O., Feldman, I., Fishman, P., Shoenfeld, Y., Rappaport, Y., Shafir, R. and Chaitchik, S. Malignant melanoma of the head and neck: clinical and immunological considerations. Amer J Clin Oncol 19: 363-367, 1996.

100. Merimsky, O., Shoenfeld, Y, Baharav, E., Zigelman, R. and Fishman, P. Reactivity to tyrosinase: Expression in cancer (melanoma and autoimmunity (vitiligo). Hum. Antibod. Hybridomas, 7: 151-156, 1996.

101. Fishman, P., Merimsky, O., Baharav, E., Shoenfeld, Y. Autoantibodies to tyrosinase: The bridge between melanoma and vitiligo. Cancer 79: 1461-1464, 1997

102. Fishman, P., Merimsky, O. and Shoenfeld, Y. Autoimmunity and cancer - beneficial relationships: a new concept for the production of human monoclonal antibodies. International J. Oncology, 10, 901-904, 1997.

103. Merimsky, O., Fishman, P. and Shoenfeld, Y. Cancer therapy with anti-idiotypic antibodies. In: Y. Shoenfeld, RC Kennedy, S. Ferrone (eds): Idiotypes in Medicine: Autoimmunity, infection and cancer. Elsevier Science BV The Netherlands, Chaper 37, pp 407-415, 1997.

104. Kamenetz, Y., Beloosesky, Y., Zeltzer, C., Gotlieb, D., Magazanik, A., Fishman, P. and Grinblat, J. Relationship between routine hematological parameters, serum IL-3, IL-6 and erythropoietin and mild anemia and degree of function in the elderly. Aging Clin. Exp. Res. Vol. 9, No. 6, 1997.

105. Blank, M., George, J., Fishman, P., Levy, Y., Toder, V., Savion, S., Barak, V., Koike, T. and Sheonfedl Y. Ciprofloxacin immunomodulation of experimental antiphospholipid syndrome associated with elevation of interleukin-3 and granulocyte-macrophage colony-stimulating factor expression. Arthritis & Rheumatism, 41, 224-232, 1998.

106. Melamed, Y., Sirota, P., Dicker, D. and Fishman, P. Superoxide anion production by neutrophils derived from peripheral blood of schizophrenic patients. Psychiatry Research , 77, 29-34, 1998.

107. Cohen-Aloro, D., Merimsky, O., Bar-Yehuda, S., Klein, B., Kayzer, S. and Fishman, P. Mononuclear cells release low molecular weight factors with anti-cancer activity: A lower level of production by cells of cancer patients. International J. Oncology, 12, 921-925, 1998.

108. Fishman, P., Bar-Yehuda, S. and Vagman, L. Adenosine and other low molecular weight factors released by muscle cells inhibit tumor cell growth: possible explanation for the rarity of metastases in muscle. Cancer Research. 58, 3181-3187, 1998.

109. Shoenfeld, Y., Sherer, Y. and Fishman, P. Interleukin-3 and pregnancy loss in antiphospholipid syndrome. Scand. J. Rheumatol. 27, 19-22, 1998.

110. Merimsky, O., Shoenfeld, Y., Fishman, P. The clinical significance of antityrosinase antibodies in melanoma and related hypopigmentary lesions. Clinical Reviews in Allergy & Immunology, 16, 227-236, 1998.

111. Shoenfeld, Y., Fishman, P. Gamma globulin inhibits tumor spread in mice. International Immunology, 11, 1247-1251, 1999.

112. Bar-Dayan, Y., Barshack, I, Blank, M., Goldberg, I., Levy, Y., Kopolovic, J., Fishman, P., Shoenfeld, Y. Antibodies to the cytoplasm, cell membrance and nuclear membrane of malignant neoplasms in pooled normal human polyspecific immunoglobulin G. International Journal of Oncology, 15, 1091-1096, 1999.

113. Bar Yehuda, S., Farbstein, T., Barer, F., Ohana, G. and Fishman, P. Oral administration of muscle derived small mulecules inhibits tumor spread while promoting normal cell growth in mice. Clin. & Exper. Metastasis 17: 531-535, 1999.

114. Bar-Dayan, Y., Barshack, I, Blank, M., Goldberg, I., Levy, Y., Kopolovic, J., Fishman, P., Shoenfeld, Y. Antibodies to the cytoplasm, cell membrance and nuclear membrane of malignant neoplasms in pooled normal human polyspecific immunoglobulin G. International Journal of Oncology, 15, 1091-1096, 1999.

115. Savion S., Blank M., Shepshelovich J., Fishman P., Shoenfeld Y., Toder V. Ciprofloxacin affects pregnancy loss in CBA/JxDBA/2J mice possibly via elevation of interleukin-3 and granulocyte colony stimulating factor production. Amer. J. of Reproductive Immunol. 44: 293-298. 2000.

116. Fishman P, Bar-Yehuda S, Farbstein T, Barer F, Ohana G. Adenosine Acts as a Chemoprotective Agent By Stimulating G-CSF Production: A Role for A1&A3 Adenosine Receptors. J. Cellular Physiol. 183: 393-398, 2000.

117. Fishman, P., Bar-Yehuda, S., Ohana, G., Pathak, S., Wasserman, L, Multani, A.S., and Barer, F. Adenosine Acts as an Inhibitor of Lymphoma Cell Growth: a Major Role for the A3 Adenosine Receptor. European J. Cancer 36:1452-1458, 2000.

118. Ohana G., Bar-Yehuda S, Barer F, Fishman P, The Differential Effect of Adenosine on Tumor and Normal Cell Growth: Focus on the A3 Adenosine Receptor J. Cellular Physiol. 186: 19-23. 2001.

119. Bar-Yehuda S., Barer F., Volfsson L., Fishman P. Resistance of Muscle to Tumor Metastases: A role for A3 adenosine receptor agonists. Neoplasia 3:125-131.2001.

120. Fishman P, Bar-Yehuda S, Barer F, Multani A.S. and Pathak S. The A3 adenosine receptor as a new target for cancer therapy and chemoprotection. Exp Cell Res. 269(2):230-236. 2001.

121. Shoenfeld Y, Levy Y, Fishman P. Shrinkage of melanoma metastases following high dose intravenous immunoglobulin treatment. Isr Med Assoc J. 3:698-699. 2001.

122. Merimsky O, Meller I, Inbar M, Bar-Yehuda S, Shoenfeld Y and Fishman P. A possible role for IVIg in the treatment of soft tissue sarcoma: a clinical case and an experimental model. Int. J Oncol. 20:839-843. 2002.

123. Fishman P, Madi L, Bar-Yehuda S, Barer F, and Khalili K. Involvement of Wnt Signaling Pathway in IB-MECA Mediated Suppression of Melanoma Cells. Oncogene 21: 4060-4064. 2002.

124. Fishman P , Bar-Yehuda S, Madi L and Cohn I. A3 Adenosine Receptor (A3AR) as a Target for Cancer Therapy. Anti-Cancer Drugs. 13:437-444. 2002.

125. Fishman P. and Bar-Yehuda S. Pharmacology and Therapeutic Applications of A3 Receptor Subtype. Curr. Top. Med. Chem. 3:463-469, 2003.

126. Bar-Yehuda, S., Madi, L., Barak, D., Mittelman, M., Ardon, E., Ochaion, A, Cohn, S., Fishman, P. Agonists to the A3 adenosine receptor induce G-CSF production via NF-kappaB activation: a new class of myeloprotective agents. Exp. Hematol.30:1390-1398, 2002.

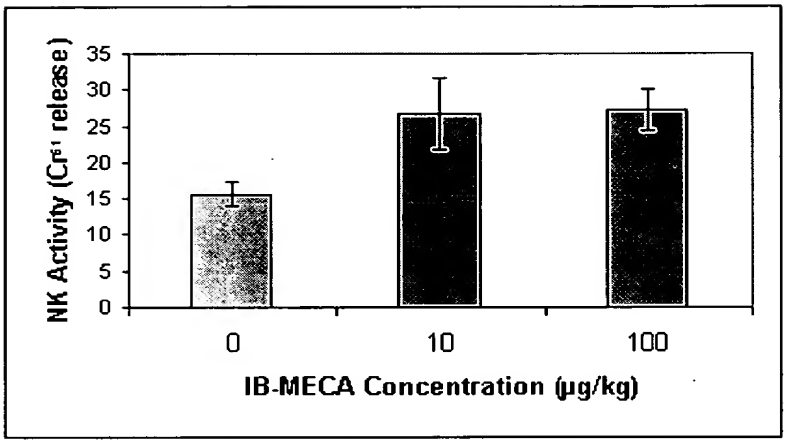
127. Baharav, E., Dubrosin, A., Fishman, P., Bar-Yehuda, S., Halpern, M., Weinberger, A. Suppression of experimental zymosan induced arthritis by intraperitoneal administration of adenosine. Drug. Dev. Res. 57 :182-186, 2002.

128. Merimsky O, Madi L, Bar-Yehuda S, Fishman P : Modulation of the A3 adenosine receptor by low agonist concentration induced anti-tumor and myelostimulation effects. Drug. Dev. Res. In Press, 2003.

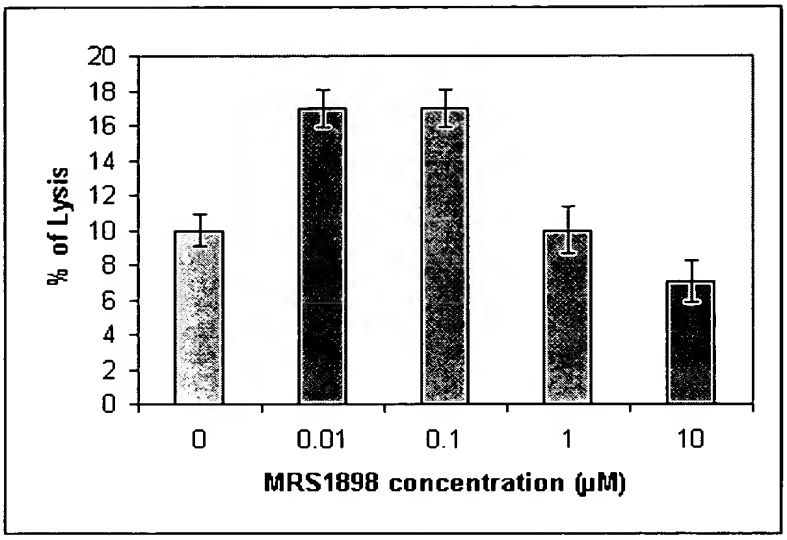
129. Fishman, P., Bar-Yehuda, S., Rath-Wolfson, L., Ardon, E., Barrer, F., Ochaion, A., Madi, L. Targeting the A3 adenosine receptor for cancer therapy: inhibition of Prostate carcinoma cell growth by A3AR agonist. Anticancer Res. In Press, 2003.

130. Fishman, P., Bar-Yehuda, S. Pharmacology and therapeutic applications of A3 receptor subtype. Curr. Top. Med. Chem. 3:463-469, 2003.

Annex B


NK Activity (Cr^{51} release)
35
30
25
20
15
10
5
0
0
10
100
IB-MECA Concentration (µg/kg)

Annex C


20
18
16
14
12
10
8
6
4
2
0
% of Lysis
0
0.01
0.1
1
10
MRS1898 concentration (µM)